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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/986,234	10/22/2001	Mitchell A. Lazar	053893-5032-01	4995

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/986,234	LAZAR, MITCHELL A.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11,23,24 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11,23,24 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks and 1.132 declaration of Inventor Lazar, filed 5/22/06, are acknowledged

2. Claims 10, 11, 23, 24, and 34 are being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10, 11, 23, 24, and 34 stand rejected under 35 U.S.C. 112, first paragraph, because the specification,
while being enabling for,
a method of treating or alleviating type II diabetes comprising administering to a mouse afflicted with type II diabetes a composition comprising an antibody that binds the resistin encoded by SEQ ID NO:2 or SEQ ID NO:4 in an amount sufficient to reduce serum glucose,
does not reasonably provide enablement for,
a method of treating or alleviating type II diabetes comprising administering to a patient (other than a mouse) afflicted with type II diabetes a composition comprising an antibody that binds the resistin encoded by SEQ ID NO:2 or SEQ ID NO:4 in an amount sufficient to reduce serum glucose.

As set forth previously, with regards to the instant claims, the level of predictability of the art (particularly in view of the state of the prior art), the amount of direction provided by the inventor, and the existence of working examples (or lack thereof), comprise the major factors to be considered. Early work with resistin showed that in rodent models upregulation of the polypeptide (SQ ID NO:2) correlated with insulin resistance and high serum glucose levels, and that a reduction of serum resistin resulted in a reduction of serum glucose levels. Accordingly, it might have been presumed that a human homologue (SEQ ID NO:4) would have a similar activity in humans. Numerous studies, however, have shown that resistin levels in humans do not correlate with insulin resistance, and thus, serum glucose levels. Note that this finding was not completely unexpected given that human and mouse resistin are just 56% identical, their gene organization is highly diverse, and the polypeptides are expressed in different tissues. Accordingly, the art shows that a method of treating or alleviating type 2 diabetes in humans, by reducing serum glucose, comprising reducing resistin levels, must be considered to be unpredictable and requiring of undue experimentation.

See, for example, Lee et al. (2003). The authors found no significant difference in resistin levels between obese nondiabetic and obese type 2 diabetic subjects (see particularly page 4852, column 2). The authors conclude, "We present one of the first human studies on circulating resistin levels and, using a highly specific ELISA, find no evidence supporting a role for serum resistin in mediating insulin resistance or reflecting obesity in humans" (page 4853, **Discussion**). Other investigators have come to similar conclusions. See, for example, Heilbronn et al. (2004), "Our study did not demonstrate an independent association between resistin and insulin sensitivity. Furthermore, although resistin was up-regulated by insulin, this effect was modest and was not observed in all subjects. Although the exact function of resistin remains unclear, this study does not support a role for resistin as a major mediator of insulin sensitivity in humans" (page 1847, **Conclusion**). In a study of Pima Indians, a population with a high prevalence of type 2 diabetes, Volarova de Courten et al. (2004) found that "high serum resistin levels were cross-sectionally associated with adiposity, but not with whole-body or hepatic insulin resistance" (page 1282, **Discussion**). As at least regards insulin resistance, even newer work continues with the same findings, see, for example, Iqbal et al. (2005), "**Serum resistin is not associated with obesity or insulin resistance in humans**" (title).

In view of the findings set forth above, the instant specification would require a significant amount of guidance to enable the claimed method. A review of the specification, however, reveals no significant guidance and no working examples of a method of treating or alleviating type 2 diabetes in humans, by reducing serum glucose, comprising reducing resistin levels. All of the examples set forth in the disclosure employ rodent models. Given that the art teaches that in this instance the results in animal models do not accurately reflect results likely to be achieved in humans, the method of the instant claims must be considered to be unpredictable and requiring of undue experimentation.

Applicant's arguments, filed 5/22/06 have been fully considered but they are not persuasive. Applicant argues that the use of the animal model in the specification is sufficient to support claims drawn to support the same teachings in humans.

As set forth in the rejection, in this instance the disclosed animal model data does not adequately support the claimed method.

Applicant reviews the disclosure.

The review is noted.

Applicant argues that working examples are not required.

While working examples are not required, enablement commensurate in scope with the claimed method is. In this instance said enablement has been found to be lacking.

Applicant cites the Inventor's 1.132 declaration.

Said declaration will be addressed here.

The Declarant begins by reviewing the Heilbronn et al. reference used in the rejection. The Declarant asserts that the reference "actually supports the contention that serum resistin plays a role in glucose homeostasis, and does not clearly address or contradict our teachings …".

The Declarant appears to have drawn different conclusions than have the authors. As set forth above, the authors concluded, "Although the exact function of resistin remains unclear, this study does not support a role for resistin as a major mediator of insulin sensitivity in humans".

The Declarant reviews the Volarova de Courten et al. reference used in the rejection. The Declarant asserts "Thus, contrary to the Examiner's contention, Volarova de Courten et al. does not clearly demonstrate or support the contention that serum resistin levels have no effect on serum glucose levels, and further does not clearly address or contradict our teachings regarding the use of anti-resistin antibodies in the treatment of Type 2 diabetes".

The Examiner made no such contention. The results reported by the authors were merely reported in the rejection.

The Declarant reviews the Iqbal et al. reference used in the rejection. The Declarant asserts that the findings of the authors were "questionable", and follows by asserting possible flaws in the method. Of interest is the assertion that the patient population was restrictive in scope.

The Declarant's position is noted. Regarding the restricted patient population, said patient population would also be encompassed by the generic method of the instant claims; thus, the method of the instant claims must be enabled for said population in addition to any other patient populations.

The Declarant reviews the Lee et al. reference used in the rejection. The Declarant asserts tat the study may have been "underpowered".

Applicant's assertion is noted.

The Declarant asserts that the combined references "are inadequate to support any contention that human resistin does not operate in type II diabetes in the same manner as mouse resistin does in mice".

It is the Examiner's position that the Inventor's position is not reasonable nor is it scientifically sound. While the Inventor may argue that different researchers may draw different conclusions, to refer to work that disagrees with his as "inadequate support for *any* contention ..." that disagrees with his appears to be a demonstration of a lack of sound scientific reasoning.

The Declarant cites a number of documents in support of the claimed method. Virtually all of them confirm that contradictory findings have been reported. While some of these references cautiously report elevated resistin in type II diabetics, it has not been established that the elevated resistin is any more than a marker for type II diabetes. And other references flatly state that said elevated resistin plays no part in insulin resistance. See for example Youn et al., "Why there are increased plasma resistin concentrations in patients with type 2 diabetes, but these have no significant association with indexes of obesity or insulin resistance, is unclear" (page 155). This sort of teaching clearly does not support the invention of the instant claims. Also see the conclusions of Fujinami et al. "Taken together, the recently described relationships of murine resistin expression with obesity and insulin resistance may not readily be translated to humans. Therefore further studies are needed to clarify their [resistins] in human metabolism" (page 62).

The Declarant/Inventor cites his own work, published some 5 years after the priority date of the instant application, wherein resistin is merely referred to as a "candidate factor" in peripheral insulin resistance. The authors report differences obtained employing different experimental mouse models, as well as significant differences between mouse and human resistin genes as well as expression. The authors conclude "Further studies that include measurements of serum levels in large populations will be required to better understand the potential involvement of resistin in the pathophysiology of obesity and diabetes in human beings", and "We are just beginning to explore the complex biology of resistin. Much more needs to be learned". Most pertinent to the

instant arguments is the Inventor/Declarant's *own* final conclusion "Finally, as human and mouse resistin appear diverse, it will be even more crucial to determine whether the physiology of mouse resistin is pertinent to human beings". Clearly, at the time of filing, the invention of the instant claims comprised no more than an idea that did not, and still does not, rise to the level of patentability.

The Declarant's final arguments are that certain drugs reduce resistin levels in humans.

Said reduction does not indicate whether resistin is an effector or a marker. Accordingly, the instant rejections have been maintained.

5. No claim is allowed.

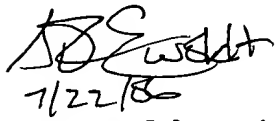
6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

8. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications

is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.



7/22/06

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